JACC Vol. 4, No. 5
November 1984:1015–20

Left Atrial Isomerism Associated With Asplenia: Prenatal Echocardiographic Detection of Complex Congenital Cardiac Malformations

PATRICIA A. STEWART, NDCT, CCPT,* ANTON E. BECKER, MD, FACC,†
JURIY W. WLADIMIROFF, MD, PHD,* CATHARINA E. ESSED, MD‡

Rotterdam, The Netherlands

Complex congenital heart disease with suspected isomerism of the atria was diagnosed in two fetuses of 20 and 29 weeks' gestation using two-dimensional and M-mode scanning techniques. The first pregnancy was terminated at 21 weeks' gestation and stillbirth occurred at 31 weeks' gestation in the second pregnancy. At postmortem examination, a thoracoabdominal discordancy was found; the spleen was absent and the arrangement of the abdominal vessels was as anticipated for asplenia, but the thoracic situs revealed a bilateral right-sided arrangement with left isomerism of the atria. The heart, otherwise, showed complex abnormalities as anticipated for asplenia.

Situs describes the arrangement of organs within the body. Generally, the situs of the abdominal organs, thoracic organs and atria will correspond, but this is not always the case and it is customary to describe each group separately (1). In situs solitus, the "morphologically right" structures are found on the right, and in situs inversus, the "morphologically right" structures are found on the left side of the body in mirror-image fashion. In some patients, however, neither situs solitus nor situs inversus exists and the organs are then isomeric. In isomerism, paired organs such as lungs and atria have bilateral morphologically right or morphologically left characteristics.

Disturbances in the development of asymmetry of organs and its relation with agenesis of the spleen were extensively documented and recognized as a developmental complex by Ivemark (2) in 1955 and by Putschar and Manion (3) in 1956. Abnormalities of the spleen gained interest among cardiologists when Van Mierop et al. (4,5) emphasized the association between absent spleen and bilateral right-sidedness and when Moller et al. (6) showed the relation between polysplenia and bilateral left-sidedness, because congenital heart disease was almost invariably present in the former and frequently less complex or even absent in the latter.

This report describes two cases of prenatal diagnosis of complex congenital heart disease with suspected atrial isomerism. Postmortem analysis revealed left atrial isomerism in association with asplenia. Van Mierop (7) mentioned experience with one case of "asplenia heart" and "polysplenia abdomen," but to our knowledge, the combination of left atrial isomerism and asplenia has not previously been reported.

Case Reports

Case 1

A healthy 23 year old woman, gravida 1, was referred at 20 weeks' gestation with fetal ascites and arrhythmia. Two-dimensional echocardiography (Hewlett-Packard 77020A) revealed a normal-sized fetus with gross ascites and hydrothorax. The heart of the fetus was thought to be situated in the left side of the chest (Fig. 1) and there was a large atrium without evidence of septation. A vessel thought to be the inferior vena cava was seen to drain into the left side of the atrium. Pulmonary venous connections were not identified. These findings suggested the presence of atrial isomerism. A single atrioventricular (AV) valve was connected to a large, left-sided hypertrophied ventricle that contracted poorly. A small chamber was visualized to the right of the main chamber and had no AV connection of its

From the *Department of Obstetrics and Gynecology, Division of Clinical Genetics, the ‡Department of Pathology, Erasmus University, Rotterdam and the †Department of Pathology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands. Manuscript received December 13, 1983; revised manuscript received May 2, 1984, accepted May 21, 1984.

Address for reprints: Patricia A. Stewart, NDCT, Department of Obstetrics and Gynecology, Academic Hospital Rotterdam–Dijkzigt, Erasmus University, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands.

0735-1097/84/$3.00

JACC Vol. 4, No. 5
November 1984:1015–20

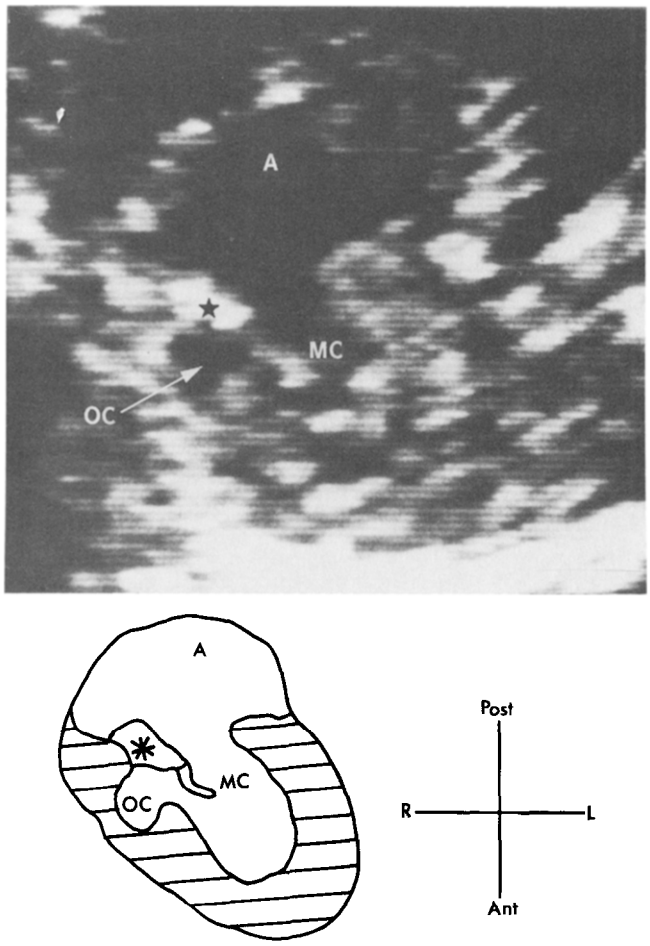


Figure 1. Case 1. Four chamber view (**top**) and line diagram (**bottom**) of the two-dimensional echocardiogram. A = large atrium without evidence of septation; Ant = anterior; L = left; MC = main chamber; OC = outlet chamber; P = posterior; R = right. * = thick echogenic area representing an absent atrioventricular connection.

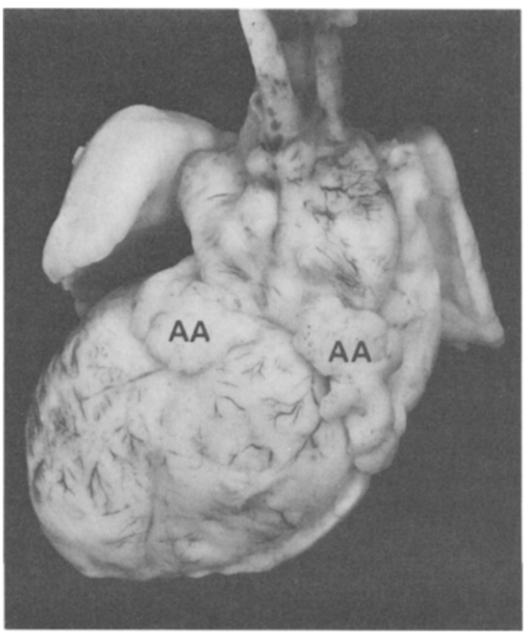
own. A thick echogenic area was seen in the region of the common AV valve and was thought to represent an absent right-sided AV connection. Both great arteries ran parallel to each other and appeared to be connected to the main chamber. Fetal M-mode echocardiography demonstrated complete heart block with an atrial rate of 105/min and a ventricular rate of 45/min.

In view of the severity of the fetal cardiac lesions, the severe congestive heart failure and the early gestational age, the parents requested termination of the pregnancy. This occurred at 21 weeks of gestation. A female fetus weighing 650 g was delivered with a distended abdomen and edema. There was a "short neck" and rocker bottom feet. No further external abnormalities were noted. Chromosome analysis revealed a normal female karyotype.

Pathologic findings. Postmortem examination revealed 100 ml of ascites and bilateral pleural effusions of 9 ml. The spleen was absent. The lungs showed a bilateral bilobed architecture with bilateral hyparterial bronchi. Contrary to the impression obtained from the echographic studies, the apex of the heart was positioned in the right chest (Fig. 2). Inspection showed that the right- and left-sided atrial appendages had the typical characteristics of a morphologic left atrium (Fig. 2). The systemic veins were abnormal with the inferior cava vein running to the left and anterior to the abdominal aorta. The vein continued as an azygos vein and drained into a left-sided superior cava vein. There was no right-sided superior cava vein. The hepatic veins drained directly into the left-sided atrium.

The heart itself showed a complex malformation. There was left atrial isomerism with an almost common atrium due to a large primum type atrial septal defect. The atrial septum was represented by a tiny shelf; the right and left pulmonary veins drained in the back of the atrium immediately adjacent to this septal vestige. The atria were almost completely separated from the underlying ventricular mass by a deeply wedged groove; the AV junctional side was small and composed of a common AV orifice. Both atria drained into a single ventricle with left ventricular trabecular characteristics (Fig. 3). A small outlet chamber was present in the left anterior shoulder of the ventricular mass, showing right ventricular trabecular characteristics. The arterial connections were concordant with the pulmonary trunk in anterior position, arising from the outlet chamber. There was subpulmonary stenosis. The aorta was in fibrous continuity with the common AV valve and arose posterior and to the

Figure 2. Case 1. Heart-lung specimen obtained at autopsy. The ventricular apex points to the right. The atrial appendages (AA) embrace the arterial pedicle and both show the characteristics of morphologic left atrial appendages.



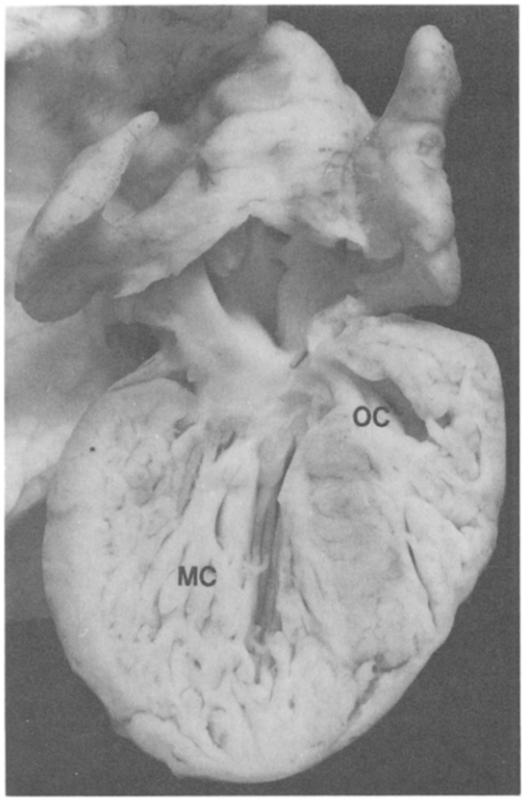


Figure 3. Case 1. Cross section through the heart. There is a common atrioventricular orifice through which both atria drain into a main chamber (MC) with left ventricular trabecular characteristics. The small outlet chamber (OC) is seen on the **left**.

right of the pulmonary trunk. The ductus arteriosus arose in its usual position from the proximal segment of the left pulmonary artery, following the bifurcation, and connected to the base of the brachiocephalic trunk, being the first artery to arise from a left-sided aortic arch. The ductus was narrowed and most likely functionally restrictive.

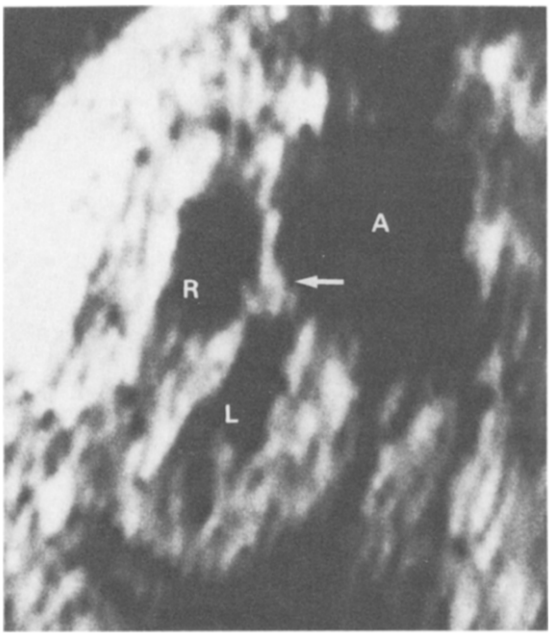
Hence, a complex cardiac malformation was present characterized by: 1) abnormal systemic and pulmonary venous connections to a "common atrium" with left atrial isomerism, 2) a univentricular AV connection through a common AV valve into a main chamber with left ventricular characteristics and a rudimentary chamber of right ventricular characteristics in the left anterior shoulder of the heart, and 3) concordant arterial connections with inverted normally related great arteries. The heart could thus be classified as a mirror-image Holmes heart.

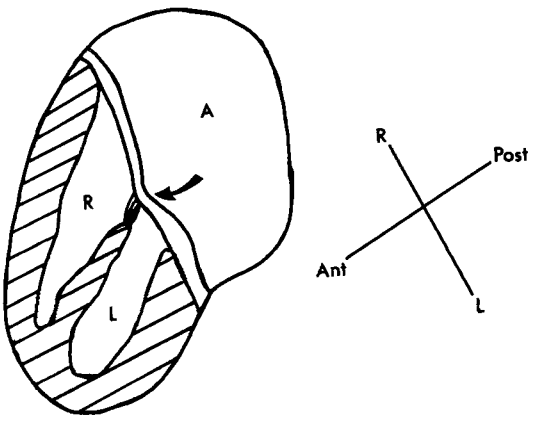
Case 2

A healthy 32 year old woman, gravida 3, was referred at 29 weeks' gestation with fetal ascites. Her previous children are normal. Two-dimensional echocardiography (Diasonics CardioVue 100) revealed polyhydramnios and a fetus with gross ascites. There was a small pericardial effusion. A large atrium without evidence of septation was identified and thought possibly to be isomeric. Vena caval and pulmonary venous connections were not identified. One large atrioventricular valve was seen to connect the single atrium to two grossly hypertrophied ventricles (Fig. 4). A bridging leaflet of the AV valve was seen to have chordal attachments to the crest of the interventricular septum. The great vessels appeared concordant and the pulmonary artery was of small caliber. The aorta was dilated and appeared to override the ventricular septum. The anatomy of tetralogy of Fallot was suspected. M-mode echocardiography indicated complete heart block with an atrial rate of 100/min and a ventricular rate of 51/min.

Pathologic findings. Stillbirth occurred at 31 weeks of gestation and a female fetus weighing 1,500 g was delivered.

Figure 4. Case 2. Four chamber view (**top**) and line diagram (**bottom**) of the two-dimensional echocardiogram. The **arrow** indicates a single atrioventricular valve which, on the two-dimensional echocardiogram, was seen to have chordal attachments to the crest of the septum. A = large atrium without evidence of septation; L = left-sided chamber; R = right-sided chamber.





JACC Vol. 4, No. 5
November 1984:1015–20

The abdomen was distended. The left small toe was abnormally implanted. No other external abnormalities were noted. There was asplenia. The heart, which had been received detached from the lungs, demonstrated left atrial isomerism. Vena caval and pulmonary venous drainage sites could not be clearly identified. The atria contained a large primum type septal defect (Fig. 5A). Both atria drained through a common AV orifice. The common valve was mainly connected to the left-sided ventricle, with only a minimal part directly emptying into the right-sided ventricle (Fig. 5B). The myocardial architecture was sponge-like, which made it difficult to ascertain the nature of the ventricles on the basis of the trabecular characteristics (Fig. 5B). The arterial connections were concordant, with fibrous continuity between the aortic valve and the common AV valve. The pulmonary trunk and ascending aorta showed normal relations. The outflow tract toward the pulmonary trunk showed an anteriorly displaced infundibular septum as in tetralogy of Fallot. There was a right aortic arch with aberrant left subclavian artery with retroesophageal position.

Discussion

In recent years, there has been increasing interest in cardiac abnormalities that occur in the setting of symmetry syndromes such as the so-called asplenia and polysplenia syndromes. The number of patients admitted to pediatric cardiac units afflicted with these anomalies is substantial and has been reported (8) as approximating 10% of all admissions.

Right versus left isomeric syndrome (asplenia versus polysplenia). Asplenia or right isomeric syndrome is almost always associated with a complex cardiac malformation (2,3,9–14). The polysplenia or left isomeric syndrome shows a more variable picture with an occasional normal heart at one end of the spectrum and severe and complex malformations at the other (6,15).

The mode of predicting these cardiac abnormalities in the neonate has gradually shifted from attempts to visualize the spleen by injection of radioactive substances to echographic detection of the abdominal vessels (16). In right and left isomerism, the vena cava and aorta are both situated on the same side of the spine. In the right isomeric syndrome, the inferior cava vein is positioned anteriorly. In the left isomeric syndrome, the major vein in the abdomen runs posteriorly. Hence, in neonates, the position of these vessels is often used as an indication of the type of cardiac abnormality to be expected.

Present cases. Our present observation of two cases of thoracoabdominal visceral discordancy indicates that exceptions occur, because the abdominal situs showed an absence of the spleen and the arrangement of the abdominal vessels was as anticipated in cases with asplenia, while the thoracic situs revealed a bilateral left-sided arrangement with

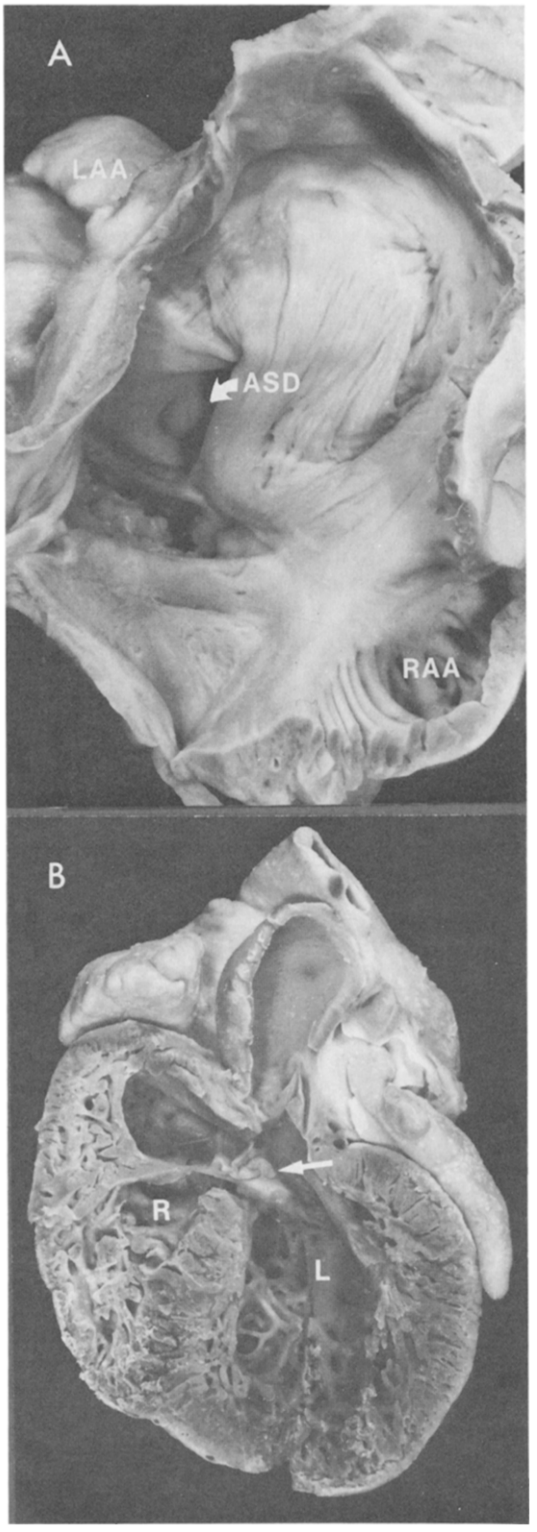


Figure 5. Case 2. Heart specimen. **A**, The inside of the atria revealing a large primum type atrial septal defect (ASD). The arrangement of the pectinate muscles, characteristic of a left atrial appendage (LAA), can be seen inside the right-sided atrial appendage (RAA). **B**, The heart cut in a plane to correspond with the two-dimensional echocardiographic view seen in Figure 4. The myocardium has a spongy appearance. The **arrow** indicates the atrioventricular valve, which for its greater part empties into the left-sided ventricle (L). R = right-sided ventricle.

left isomerism of the atria. Apart from the morphology of the atrial appendages, however, the cardiac malformations in both patients showed the complexity anticipated for asplenia. Thus far, our experience indicates that these cases are unusual, and we have been unable to find any previous reports of this combination of defects. However, other discrepancies in situs have previously been reported in patients with asplenia. Putschar and Manion (3) emphasized that absence of the spleen could occur with and without associated malformations and with various types of abnormalities in situs. A discordant anatomy between bronchi and atria in asplenia has been documented (17) and "asplenia-like" visceral abnormalities have been described (18) with a normal spleen and even in the presence of multiple spleens. Indeed, it is clear that "crossover" cases exist between the classic examples of the asplenia and polysplenia syndromes (19), as previously outlined (4–6). From that point of view, therefore, one should avoid diagnosing one of these syndromes on the basis of a single item, be that the presence or absence of the spleen, the position of the abdominal vessels or the anatomy of bronchi and atrial appendages.

Prognosis. Patients with "classic" asplenia have a poor prognosis and 79 to 94% die before the age of 1 year (5,15), with congestive heart failure and anoxia being major causes of death. The risk of sudden and severe infection is high. The two fetuses in this report showed evidence of severe congestive heart failure and this was most likely the cause of death in Case 2. Moreover, congestive heart failure would probably have caused the death of the fetus in Case 1 if the pregnancy had not been terminated at 21 weeks of gestation. It has been a major concern that the echocardiogram in this patient was mistakenly interpreted as showing the heart with the apex in the left side of the chest, while the autopsy unequivocally showed the apex to be on the right. Careful review of the videotapes still showed the heart to be apparently left-sided. We have no satisfactory explanation for this phenomenon other than to suggest that the precise prenatal echographic identification of the position of the heart may be hampered in patients with severe hydrothorax and ascites.

Implications. It remains to be answered whether these findings constitute a new entity or whether the combination of defects reported represents a lethal group of abnormalities that tends to remain undetected because death occurs in utero and postmortem analysis is usually not carried out. Recent advances in ultrasound equipment have shown that detailed analysis of the fetal heart is possible (20–22), and prenatal echographic evaluation of the heart is increasing. In fact, the prenatal diagnosis of severe congenital cardiac abnormalities with the suspicion of atrial isomerism resulted in precise postmortem investigation in our cases. On that basis, we may perhaps postulate that more cases with this particular anatomic arrangement may be identified in the future with the increasing use of prenatal echocardiography.

We are grateful to J. H. Deelen, MD, Onze Lieve Vrouwe Gasthuis, Amsterdam for referring Case 1, R. de Boer, MD, Groot Ziekengasthuis's, Hertogenbosch for referring Case 2 and Alize Bijl and Marsha Schenker for secretarial assistance.

References

1. Becker AE, Anderson RH. Pathology of Congenital Heart Disease. Postgraduate Pathology Series. London: Butterworths, 1981:211.
2. Ivemark IB. Implication of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood: analysis of the heart malformations in splenic agenesis syndrome, with fourteen new cases. Acta Paediatrica 1955;44(suppl 104):1-110.
3. Putschar WG, Manion WC. Congenital absence of the spleen and associated anomalies. Am J Clin Pathol 1956;26:429–70.
4. Van Mierop LHS, Wigglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. Lab Invest 1962;11:1303–15.
5. Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndrome. Birth Defects: Original Article Series 1972;1:74–82.
6. Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral "left-sidedness." Circulation 1967;36:789–99.
7. Van Mierop LHS. Discussion on Chapter 19. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. Paediatric Cardiology, vol 5. Edinburgh: Churchill Livingstone, 1983:203–4.
8. Deanfield JE, Leanage R, Stroobant J, Chrispin AR, Taylor JFN, Macartney FJ. Use of high kilovoltage filtered beam radiographs for detection of bronchial situs in infants and young children. Br Heart J 1980;44:577–83.
9. Polhemus DW, Schafer WB. Congenital absence of the spleen: syndrome with atrioventricularis and situs inversus. Pediatrics 1952;9:696–708.
10. Polhemus DW, Schafer WB. Congenital absence of the spleen. Pediatrics 1955;16:495–7.
11. Schonfeld EA, Frischman B. Syndrome of spleen agenesis, defects of the heart and vessels and situs inversus. Helvetica Paediatrica Acta 1958;13:636–40.
12. Ruttenberg HD, Neufeld HN, Lucas RV Jr, et al. Syndrome of congenital cardiac disease with asplenia: distinction from other forms of congenital heart disease. Am J Cardiol 1964;13:387–406.
13. Landing BH, Lawrence TK, Payne VC Jr, Wells TR. Bronchial anatomy in syndromes with abnormal visceral situs, abnormal spleen and congenital heart disease. Am J Cardiol 1971;28:456–62.
14. Silver W, Steier M, Chandra N. Asplenia syndrome with congenital heart disease and tetralogy of Fallot in siblings. Am J Cardiol 1972;30:91–4.
15. Rose V, Izukawa T, Moës CAF. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. Br Heart J 1975;37:840–52.
16. Huhta JC, Smallhorn JF, Macartney FJ. Two dimensional echocardiographic diagnosis of situs. Br Heart J 1982;48:97–108.
17. Caruso G, Becker AE. How to determine atrial situs? Considerations initiated by 3 cases of absent spleen with a discordant anatomy between bronchi and atria. Br Heart J 1979;41:559–67.
18. Freedom RM. Aortic valve and arch anomalies in the congenital asplenia syndrome. Case report, literature review and re-examination of the embryology of the congenital asplenia syndrome. Hopkins Med J 1974;135:124–35.
19. Van Praagh R, Weinberg PM, Matsuoka R, Van Praagh S. Malpositions of the heart. In: Adams FH, Emmanouilides GC, eds. Moss' Heart Disease in Infants, Children and Adolescents. 3rd ed. Baltimore: Williams & Wilkins, 1983:424.

20. Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C, Giles H. Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. Circulation 1980;62:799–806.

21. Allan LD, Tynan M, Campbell S, Anderson RH. Normal fetal cardiac anatomy—a basis for the echocardiographic detection of abnormalities. Prenat Diagn 1981;1:131–9.

22. Stewart PA, Wladimiroff JS, Essed CE. Prenatal ultrasound diagnosis of congenital heart disease associated with intrauterine growth retardation. Prenat Diagn 1983;3:279–85.